REMARKS

Status of the Claims

Claims 1, 3-9, and 11-22 are pending in the present application. Claims 2 and 10 were previously canceled. Claims 6, 14, and 18-21 are withdrawn as directed to a non-elected invention. In view of the following remarks, reconsideration of the present application is respectfully requested.

Issues under 35 U.S.C. § 103(a)

Claims 1, 3, 4, 7-9, 11, 12, 15-17, and 22 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious over Kessels *et al.*, *Nature Immunology*, 2:957-961, ("Kessels") in view of Fujio *et al.*, *Journal of Immunology*, 165:528-532, ("Fujio"), Tsuji *et al.*, *Cancer Science*, 2003, 94:389-393, ("Tsuji"), and Nishimura, *Cancer Treatment and Host*, 12:363-373, ("Nishimura"), *see* Office Action, pages 2-7. For the reasons set forth below, Applicants respectfully traverse.

Claims 1, 5, 9, and 13 are also rejected under 35 U.S.C. § 103(a) as allegedly obvious over Kessels, Fujio, Tsuji, and Nishimura, and in view of U.S. Patent No. 7,323,181 to Gaiger *et al.*, ("Gaiger"), *see* Office Action, pages 8-11. For the reasons set forth below, Applicants respectfully traverse.

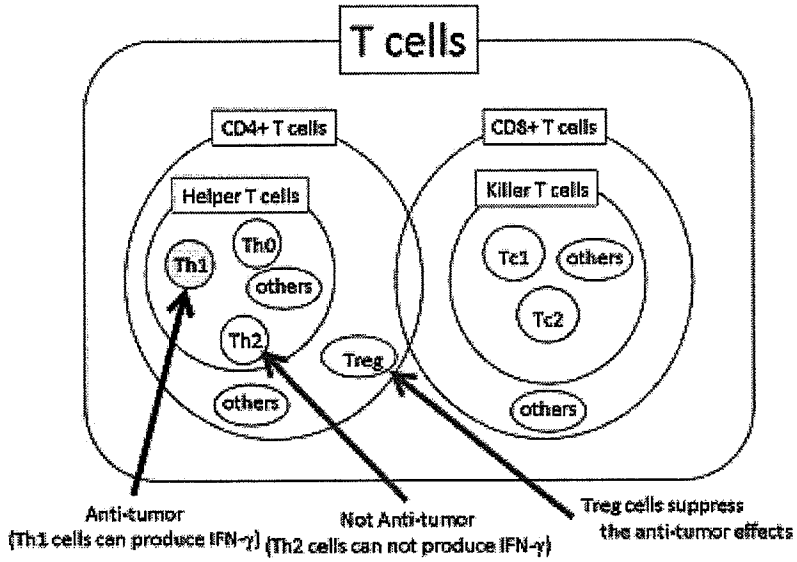
The Claims are not rendered obvious by the cited references

The Classification of T Cells

The present invention provides a novel, non-obvious technology to induce helper T cells. However, on page 7, lines 1-2 of the present Office Action, the Office Action states that "whether the Th1 cells or Tcl cells are induced or activated or not appears to be irrelevant to the instant invention", *see* page 7, lines 1-2 of the instant Office Action. Accordingly, the Office Action appears to indicate that helper T cells and killer T cell are the same in that they are both classified as "T cells." Applicants respectfully disagree with these comments, the interpretation of the instant claims, and the apparent mischaracterization of the state of the art. Applicants submit that the comments in the Office Action are clearly inconsistent with the general knowledge in the art.

Applicants note that the immune response is greatly impacted by whether or not helper T cells or Tc1 cells are induced or activated. Tcl cells are totally different from helper T cells.

That is, Tc1 cells and helper T1 cells are distinguished by, *inter alia*, cellular function, induction properties, ability to produce cytokines, and intracellular signal transduction pathways. Applicants further note that CD4+ cells are also not equivalent to Th1 cells (helper T1 cells). Applicants submit herewith the below diagram, which describes the classification of immune cells (T cells).



In view of the foregoing, Applicants submit that those of ordinary skill in the art are well aware that helper T cells and killer (Tc) cells are completely different cell types.

The differences between the features of present invention and the cited references.

Applicants submit that the claimed invention could not have been achieved from the combination of cited references since an ordinary artisan could not have reasonably expected that tumor antigen specific helper T1 (Th1) cells could have been induced and proliferated according to the processes described in the pending claims. For the Examiner's convenience, the Table below is presented to show the differences between the present invention and the cited references in terms of the cell types, introduced genes and immunogens, and the resulting cell function.

	Type of Cell	**Gene and Immunogen**	**Result**
The Present Invention	helper T1 cell (Th1 cell)	Class I-restricted TCR tumor antigen	tumor antigen specific helper T1 (Th1) cells were induced and proliferated
Kessels	T cells (*a group of T cells without discriminating between CD4+ and CD8+*)	Class I-restricted TCR influenza virus (IV)	T cells expressing TCR were obtained, but CD4+ cells specific to IV were not
Fujio	TG40 cell (*a fusion cell derived from helper T cell and a cancer cell*)	Class II-restricted TCR tumor antigen	tumor antigen specific CD4+ cells were induced and proliferated
Tsuji	killer (Tc) cell	Class I-restricted TCR tumor antigen	tumor antigen specific Tc cells were induced and proliferated

As noted above, an ordinary artisan could not have reasonably predicted that the above-described technical features of the present invention could have been achieved from any combination of the cited references. In particular, the present invention differs from Kessels in the cell types, introduced immunogen, and function of the resulting cells. More importantly, as described further below, Kessels was unable to obtain antigen specific helper T cells using Class I-restricted TCR influenza virus (IV). Such results are contrary to the results observed with the instantly claimed processes. Moreover, Fujio, Tsuji, Nishimura, and Gaiger do not remedy the deficiencies of Kessels, *see* below.

Kessels teaches away from the claimed invention

Applicants submit that it is not reasonable to cite Kessels as the primary (closest) prior art. Applicants reiterate, as described in the response submitted on November 15, 2011, that Kessels describes transducing a virus antigen-specific, class I-restricted T Cell Receptor (TCR) gene into killer T cells, or into whole spleen cells containing helper T cells, *see* from page 958,

left-column, line 3, and Fig. 1 of Kessels. The results show that killer T cells, specific to the virus antigen, were induced, *see* Fig. 2 and Fig. 3, from page 958, left-column, line 3 of Kessels. However, no expansion of helper T cells (CD4+ T cells), which were specific to the virus antigen, were detected, *see* from page 959, left-column, line 9 of Kessels. Regarding the lack of induction of helper T1 cells, the authors suggest that cooperation of the transduced class I-restricted TCR with the CD4 antigen of the helper T cells and proper signaling toward the helper T cells did not work well, *see* from page 959, left column, line 14 of Kessels. Accordingly, Kessels teaches that helper T1 cells could not be induced.

In reply to Applicants' argument that Kessels fails to obtain CD4+ T cells, the Examiner states as follows: "[a]lthough there is no expansion *(note: it means cell proliferation upon stimulated)* of CD4+ T cells taught by Kessels, however, Kessels points out that CD4+ T cells (helper T cells) may require expression of both MHC class I- and class II-restricted TCR for the induction of CD4+ T cell immunity against tumor antigen", *see* Office Action, page 6, lines 16-19 and page 10, lines 12-15.

The Examiner's comments appear to be based upon the following disclosure in Kessels "[t]his lack of expansion of TCR-transduced CD4+ T cells was consistent with the idea that CD4 coreceptor binding and signaling is required for proper T cell activation; it suggests that, for the simultaneous induction of CD4+ T cell immunity, coapplication of retroviruses encoding MHC Class II-restricted TCRs may be considered", *see* Office Action, page 4, lines 13-17

Applicants submit that the Examiner has misinterpreted the above-described passage in Kessels. CD4+ T cells intrinsically express Class II-restricted TCR. Kessels introduced an antigen specific "Class I" -restricted TCR into a group of T cells including CD4+ T cells. If expression of both MHC Class I- and Class II-restricted TCRs is required, then antigen specific CD4+T cells should have been induced in Kessels; however such induction did not occur. This means that Kessels' results suggest that co-application (simultaneous introduction) of both of the antigen specific ("virus antigen specific" in Kessels) Class I and Class II TCRs is essential.

In contrast, the present invention does not require the simultaneous introduction of the antigen specific Class II TCR. According to the present invention, antigen specific Class I-restricted TCR is introduced into helper T1 (Th1) cells, which have not been conditioned for antigen specificity, to provide antigen specific helper T1 (Thl) cells. Therefore, the present invention has a technical feature which is different from (or contrary to) the suggestion by

Kessels and achieves different results. Thus, Kessels teaches away from the present invention.

As Applicants explained in the November 15, 2010 response and as reiterated above, Kessels fails to induce CD4+ T cells. Nevertheless, the Examiner appears to believe that CD4+T cells were induced in Kessels: "Kessels teaches retroviral transduction of mouse splenocytes, which includes both CD8+ T cells and CD4+ T cells", *see* Office Action, page 10, lines 3-4. Applicants submit that what the authors obtained was a group of T cells (the T cells are not specified as "helper T cells"), which display the introduced Class I-restricted TCR on the surface of the cells. However, the authors failed to obtain modified T cells, where the TCR recognizes a certain immunogen as a ligand, and transduces signals into the cells, such that the T cells exhibit specificity to that immunogen. Applicants submit that Kessels' work is analogous to merely obtaining recombinant *E. coli* cells, which express a TCR gene.

Fujio, Tsuji, Nishimura, and Gaiger do not remedy the deficiencies of Kessels

Fujio does not remedy the deficiencies of Kessels. Fujio discloses that a "Class II"-restricted TCR is introduced into TG40 cells (a fusion cell derived from a helper T cell and a cancer cell) to obtain a tumor antigen specific CD4+ cells. If the "TG40 cell" is interpreted to be a "helper T cell", Fujio's result is not surprising for the following reasons. A helper T cell functionally expresses Class II-restricted TCR in nature (as discussed above), and has a signal transduction pathway for a Class II-restricted TCR. When an exogeneous Class II-restricted TCR is introduced into helper T cells, the function of the cell will, of course, be exerted.

Tsuji also fails to remedy the deficiencies of Kessels and Fujio. Tsuji discloses that a class I-restricted TCR gene is introduced into killer T cells, *see* Tsuji, from page 389, right-column, line 3 from the bottom, to induce functional killer T cells, *see also* Figs. 3 and 4 of Tsuji. Applicants note that killer T cells have completely different properties and functions from helper T cells. For example, a killer T cell is a CD8-positive T cell and a helper T cell is a CD4-positive T cell. Accordingly, any findings obtained from transduction experiments using killer T cells would not have allowed an ordinary artisan to reasonably predict that functional helper T1 cells could have been prepared by transducing helper T cells with a TCR gene. Also, as indicated above, helper T1 cells cannot be discussed in parallel with killer (Tc) cells.

Nishimura also fails to remedy the deficiencies of Kessels, Fujio, and Tsuji. Nishimura merely suggests that helper T1 cells will generally be effective in immunotherapy of cancers.

Nishimura does not provide any experimental procedures or describe any results regarding the introduction of TCR. Moreover, Nishimura does not suggest induction of tumor antigen specific helper T1 (Th1) cells.

Gaiger also fails to remedy the deficiencies of the above-cited references and is merely cited to for describing cancer-associated antigen Wilms' tumor 1 (WT1).

Unexpected Results

In contrast to the cited references, the instantly claim methods result in the expression of Class I-restricted TCR in helper T1 cells, which intrinsically do not express Class I-restricted TCR, and have a signal transduction pathway the same as a Class II-restricted-TCR. Those of ordinary skill in the art could not have predicted such a surprising result from Fujio, or from Tsujii, which discloses different type of cells (*i.e.* killer T cells), and much less from Kessels which suggests the possibility of failure.

Accordingly, those skilled in the art would not have achieved the instant invention with a reasonable expectation of success from the cited references.

In view of the foregoing, the claims are not rendered obvious by the combination of Kessels, Fujio, Tsujii, Nishimura and Gaiger. Accordingly, withdrawal of the rejections is respectfully requested.

CONCLUSION

In view of the above remarks, Applicants believe the instant application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Linda T. Parker, Ph.D., Registration No. 46,046 at the telephone number of the undersigned below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

Dated: MAY 12 2011

Respectfully submitted,

Reg No. 44,046

By Linda Parker
for Gerald M. Murphy, Jr.
Registration No.: 28977
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road, Suite 100 East
P.O. Box 747
Falls Church, VA 22040-0747
703-205-8000